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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/825,769	04/04/2001	Milan S. Blake	NV1932	3657

7590 11/12/2004

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EXAMINER	
FORD, VANESSA L	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 11/12/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	09/825,769	BLAKE ET AL.	
	Examiner	Art Unit	
	Vanessa L. Ford	1645	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 10 August 2004 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☐ The period for reply expires _____months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.
ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☒ A Notice of Appeal was filed on *10 August 2004*. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☐ The proposed amendment(s) will not be entered because:

   (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

   (b) ☐ they raise the issue of new matter (see Note below);

   (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____.

3. ☐ Applicant's reply has overcome the following rejection(s): _____.

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *see Advisory attachment.*.

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☒ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: *NONE*.

   Claim(s) objected to: *NONE*.

   Claim(s) rejected: *13-17*.

   Claim(s) withdrawn from consideration: _____.

8. ☒ The drawing correction filed on *30 September 2003* is a)☒ approved or b)☐ disapproved by the Examiner.

9. ☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10. ☒ Other: *Advisory attachment.*

Advisory Action Attachment

1. This action is responsive to Applicant's response filed August 10, 2004 is acknowledged.

Rejections Maintained

2. The rejection of claims under 35 U.S.C. 112, first paragraph is maintained for the reasons set forth on pages 3-5, paragraph 6 of the Final Office Action.

The rejection was on the grounds that the claims are rejected under 35 U.S.C. 112, first paragraph as containing subject matter which lacks written description in the specification in such a way as to enable one skilled in the art to which it pertains or with which it is most nearly connected to make and/or use the invention.

The claims are drawn to a method for producing PT comprising a *B. pertussis* cysteine desulfinase knockout mutant in a *B. pertussis* culture medium and isolating the PT from the culture medium and a method of enhanced production of PT comprising cultivating B. *pertussis* cysteine desulfinase knockout mutant.

The claims broadly encompass a genus of cysteine desulfinase genes. There is substantial variability among the species of cysteine desulfinase genes encompassed within the scope of the claims. The specification does not place any structure limitations on the cysteine desulfinase gene. The scope of the claims include numerous structural variants and the genus is highly variant because a significant number of structural difference between genus members is permitted. Structural features that could distinguish compounds in the genus from others in the gene class are missing from the disclosure and the claims. No common structural attributes identify the members of the genus. Since there is no structure in the claim to define the cysteine desulfinase gene, the claimed genus includes cysteine desulfinase genes produced by other microorganisms. For Example, Mihara et al, *(The Journal of Biological Chemistry, Vol. 272, No. 36, p. 22417-22424)* teach that *Escherichia coli* appears to contain three nifS-like genes which encode NIFS-like protein (page 22417). Mihara et al teach that the NIFS-like proteins encoded by the nifS gene of *E. coli* has cysteine desulfurase activities. Mihara et al teach that nifS and NIFS-like proteins are found in a number of microorganisms (see Table III). Since the claimed genus encompasses genes of other microorganisms and genes yet to be discovered, the mere recitation of a "cysteine desulfinase knockout mutant" does not provide an adequate written description of the claimed genus since no structure accompanies the function of cysteine desulfurase activity. One skilled in the art would not recognize from the claimed disclosure that the applicant was in possession of the genus of nucleic acid sequences that are required to use the claimed method of producing PT comprising a *B. pertussis* cysteine desulfinase knockout mutant in a *B. pertussis* culture medium and isolating the PT from the culture medium. The recitation of "cysteine desulfinase

knockout mutant" does not convey a common structure. As such, generic nucleic acid sequences that are unrelated via structure are highly variant and not conveyed by way of the written description in the specification at the time of filing. Therefore, the specification lacks written description for the highly variant genus of nucleic acid sequences that have cysteine desulfinase activity and one of skill in the would not recognize that Applicants had possession of the genus of the claimed genes for use in the method as instantly claimed method.

Applicant urges that independent claim 1 pertains to a method of producing pertussis toxin comprising cultivating *Bordetella pertussis* bacteria that lack cysteine desulfinase activity. Applicant urges that the claims do not require the cysteine desulfinase gene or any structure or variant thereof in the claimed invention. Applicant urges Mihara et al is incorporated into the specification by reference. Applicant urges that the genes to knocked out may be any gene provided that at least some sequence information on the DNA to be disrupted is available to use in the preparation of the knockout construct. Applicant urges that techniques such as transposon mutagenesis or irradiation to knockout a known or unknown gene to obtain defective phenotypes are known in the art. Applicant refers to the Mosqueda et al reference to support their position.

Applicant's arguments filed August 10, 2004 have been fully considered but they are not persuasive. The claimed method broadly encompasses the use a genus of cysteine desulfinase genes. Although the Applicant is not claiming cysteine desulfinase genes, one skilled in the art must identify which sequences within the *Bordetella pertussis* can be modified to arrive at a *Bordetella* mutant that "lacks cysteine desulfinase activity" and can produce pertussis toxin. It should be noted that a review of

the specification indicates that the elements which are not particularly described, including regulatory element and untranslated regions are essential to the function of the claimed invention. The claims recite a function (i.e. lacking cysteine desulfinase activity) is essential to the claimed method. While techniques such as transposon mutagenesis or irradiation to knockout a known gene to obtain defective phenotypes are known in the art, it is not routine in the art to screen for multiple insertions or multiple modifications of other types and the positions within the nucleic acid's sequence where nucleic acids modifications can be made with a reasonable expectation of success in obtaining the desired activity are limited in any nucleic acid molecule and the result of such modifications is unpredictable based on the instant disclosure. What modifications are made within the *Bordetella* mutant that makes the bacterium lack cysteine desulfinase activity? Applicant admits in the after-final response that "the gene to be knocked out may be any gene provided that at least some sequence information on the DNA to be disrupted is available to use in the preparation of the knockout construct". How could one of skill in the art conclude that Applicant's were in possession of the genus of cysteine desulfinase genes to be used in the claimed method, if any gene can be used in the claimed method? There is no correlation between the function (i.e. lacking cysteine desulfinase activity) and the structure of the non-described regulatory elements and untranslated regions of the genes used to arrive at the mutants required for the claimed method.

To address Applicant's comments regarding the Mihara et al reference, this reference was used to convey that any cysteine desulfinase gene can be used in the

claimed method. Applicant asserts that using the teachings of the in Mosqueda et al reference, one of skill in the art could select for a kanamycin resistant *Bordetella*, a marker encoded by the transposon and screen the transposon mutants for those lacking cysteine desulfinase activity. It should be remembered that the claims are directed to a method of producing pertussis toxin and not a method of producing or screening for *Bordetella* mutants that lack cysteine desulfinase activity. The specification lacks written description as what modifications are made within the cysteine desulfinase gene to arrive at *Bordetella* mutants that produce pertussis toxin. One skilled in the art would not recognize that Applicants had possession of the genus of *Bordetella* mutants (comprising modified or altered cysteine desulfinase genes) that can be used in the claimed method. Therefore, one skilled in the art would not recognize that Applicants were in possession of the claimed method of producing pertussis toxin by what is described in the instant disclosure. Applicants have not met their burden under 35 U.S.C. 112 first paragraph, written description requirement.

3. Any inquiry of the general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308–0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Office Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for the Group 1600 is (703) 308-4242.

Any inquiry concerning this communication from the examiner should be directed to Vanessa L. Ford, whose telephone number is (571) 272-0857. The examiner can normally be reached on Monday – Friday from 9:00 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached at (571) 272–0864.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov./>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Vanessa L. Ford
Biotechnology Patent Examiner
October 30, 2004

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